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Subclinical symptoms in mood disorders: pathophysiological and therapeutic implications

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ABSTRACT

Background. The aim of this review was to survey the available literature on prodromal and residual symptoms of unipolar major depression and bipolar disorder.

Methods. Both a computerized (Medline) and a manual search of the literature were performed.

Results. In a substantial proportion of patients with affective disorders a prodromal phase can be identified. Most patients report residual symptoms despite successful treatment. Residual symptoms upon remission have a strong prognostic value. There appears to be a relationship between residual and prodromal symptomatology (the rollback phenomenon).

Conclusions. Appraisal of subclinical symptomatology in mood disorders has important implications for pathophysiological models of disease and relapse prevention. In depression, specific treatment of residual symptoms may improve long-term outcome, by acting on those residual symptoms that progress to become prodromes of relapse. In bipolar disorder, decrease of subclinical fluctuations and improvement of level of functioning by specific therapeutic strategies may add to the benefits provided by lithium prophylaxis.

INTRODUCTION

Current emphasis in psychiatry is on cross-sectional assessment of symptoms resulting in diagnostic criteria and on co-morbidity. This latter takes the form of both co-occurrence of Axis I psychiatric disorders and association of Axis I and II disturbances. Longitudinal appraisal of prodromes, the fully developed disorder and residual states is largely neglected (Fava & Kellner, 1991, 1993). Such neglect is particularly impressive in mood disorders. The basic assumption is that subclinical symptomatology is likely to be devoid of substantial clinical interest. The aim of this review was to provide evidence for challenging this assumption. Subclinical symptomatology associated with unipolar depression and bipolar disorder will be surveyed, after examining the major methodological aspects of this research area. Subclinical symptomatology not directly associated with these disorders – such as subsyndromal symptomatic depression – will not be discussed here, although its research findings support those of this review (Judd, 1994).

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METHODOLOGICAL ISSUES

Several methodological problems are involved in the exploration of subclinical symptomatology in affective disorders. These include definition, measurement, assessment, overlaps with other psychiatric variables, and longitudinal role.

Definition

In clinical medicine, subclinical symptomatology may consist of three types of symptoms: prodromes; residual symptomatology; and subclinical fluctuations in chronic disorders.

Prodromes can be identified with the early symptoms and signs of a disease. The prodromal phase connotes a time interval between the onset of prodromal symptoms and the onset of the characteristic manifestations of the fully developed illness. Infectious diseases provide simple models for the differences between the phases. With some infections, the onset of the illness is abrupt and prodromal symptoms last only a few hours, such as in acute upper respiratory tract infections. In others, the prodromal phase can be long, such as in viral hepatitis. The opportunity of taking advantage of the warning period provided by early symptoms has been emphasized in several life-threatening disorders such as myocardial infarction (Klaeboe *et al*. 1987), subarachnoid haemorrhage (Ostergaard, 1990) and lymphomas (Krolick *et al*. 1990). Prodromes may range from subject symptoms to laboratory markers. In recurring illnesses, such as bronchial asthma (Beer *et al*. 1987), it was found that each individual tended to have a constant set of prodromal findings throughout episodes.

Residual symptoms – defined as the persistence of symptoms and signs despite apparent remission or recovery – are frequently observed in clinical medicine. Infectious diseases, also in this case, may provide several examples of residual symptomatology after the acute illness has abated. At times, residual symptoms may include behavioural disturbances (Imboden *et al*. 1961). Often, residual symptoms and signs have predictive value as to the likelihood of recurrence, such as post-surgical urinary cortisol and plasma ACTH levels in Cushing's disease (Sonino *et al*. 1996).

Finally, in any chronic and recurring medical illness, subclinical fluctuations – both in terms of symptomatology and laboratory markers – may occur. Their clinical significance is very variable as to long-term outcome and likelihood of relapse.

Measurement

Subclinical symptoms are, by definition, milder than those of the full clinical syndrome. As a result, the capacity of the assessment instrument to measure small increments or small changes near the normal end of the spectrum becomes important. The ability of a rating or self-rating scale to discriminate between different groups of patients suffering from the same illness (e.g. depressed in-patients and out-patients) and to reflect changes in experiments in therapeutics such as drug trials in which the drug effects are small may indicate its degree of sensitivity (Kellner, 1992). Unfortunately, researchers tend to focus on the psychometric characteristics of validity and reliability and to neglect sensitivity. They may thus employ inadequately sensitive instruments to establish lack of significant symptomatology (Fava, 1992*a*). The target of the instruments employed is equally important. For instance, in a naive conceptualization, yet the one implicitly endorsed by DSM, well-being and distress may be seen as mutually exclusive (i.e. well-being is lack of distress). However, there is evidence to question this view (Ryff, 1989; Fava, 1992*b*; Bech *et al*. 1996; Ryff & Singer, 1996). A recent study found that quality of life measurements, and not symptomatic ratings, could predict recurrence of depression (Thunedborg *et al*. 1995).

Measurement need not be limited to psychometric tools. The past decade has witnessed an upsurge of research on biological markers in affective disorders and a joint use of biological and psychometric tools may be feasible.

Assessment

The detection of subclinical symptomatology may be retrospective as well as prospective. In this sense, there are several similarities with the methodological problems of research of life events (Paykel, 1987). Retrospective studies have obvious inherent risks – in particular, biased or distorted recall. The more distant the period of recall, the more likely is the life change to be underestimated and the accuracy of recall to be inversely proportional to the remoteness of the time period to be recalled (Hurst, 1979). If the patient or relatives are questioned about events during a crisis, they are likely to distort the meaning and seriousness of the events (Kaplan, 1970). Anxious patients receiving an active drug were found to be more likely to report positive events and less likely to report negative events than patients receiving placebo (Lipman *et al*. 1965). Similarly, memories of experiences that had been unhappy are more likely to be retrieved on the more depressed occasion than on the less depressed occasion in patients with diurnal mood variation (Clark & Teasdale, 1982). In life

events research, a delay in the interview until the acute disturbance has passed (Paykel *et al*. 1969; Fava *et al*. 1981), results in a less distorted history.

Problems of biased recall and 'effort after meaning' (Whitehorn, 1947) may particularly affect retrospective detection of prodromal symptoms in acutely ill psychiatric patients. The study on prodromal symptoms of schizophrenia by Herz & Melville (1980) provided seminal methodological insights in this direction. Satisfactory inter-rater reliability was obtained in panic disorder (Fava *et al*. 1988*a*) and psychotic patients (Jackson *et al*. 1994) with semistructured interviews that allow detailed probing and cross-checking with relatives. Delay of interview to clinical remission was also found to be important.

The assessment of residual symptoms is inextricably linked to the definition of remission and recovery (Frank *et al*. 1991; Angst *et al*. 1996; Fava, 1996). For instance, attainment of a designated percentage change over baseline on a symptom rating scale such as the Hamilton Depression Rating Scale frequently underlies the definition of response in major depression. The arbitrary nature of these decisions along a response continuum that may range from refractory depression to full remission via partial remission is obvious (Fava, 1996).

Overlaps with other psychiatric variables

There are three main sources of overlap between subclinical symptomatology, whether prodromal or residual, and other psychiatric variables. One involves pre-morbid traits that may be confused with prodromal and residual symptoms. Unfortunately, the state–trait dichotomy and its psychometric counterparts appear to be situated on a continuum with blurred borders that do not permit clear-cut differentiation (Fava, 1996). For instance, certain personality traits may entail enduring long-term characteristic modes of feeling, thinking and behaving in the course of depression, whereas antidepressant treatment may be beneficial in the modification of other personality traits, which are therefore subject to state influences (Fava, M. *et al*. 1994; Peselow *et al*. 1994; Chien & Dunner, 1996; Black & Sheline, 1997). A modality for overcoming this overlap – at least in part – is to include, among subclinical symptoms, only those symptoms with a clear onset, as was performed in some studies on affective prodromes (Fava *et al*. 1988*a*, 1990).

Another confusing variable may be co-morbidity. At times, when two mental disorders occur jointly, there is hierarchical relationship, whereby successful treatment of the primary disorder may result in recovery from both. For instance, behavioural treatment of agoraphobia associated with panic attacks may result in recovery from co-occurring hypochondriasis, without any specific treatment for the latter (Fava *et al*. 1988*b*). At other times, treatment of one disorder does not result in disappearance of co-morbidity. For instance, successful treatment of depression may not affect pre-existing anxiety disturbances. Co-morbid anxiety disturbances may thus be detected in the residual phase of depression.

A third issue involves the concept of hierarchical order, whereby certain psychiatric features are given precedence in diagnosis over others or are viewed as antecedent to others. Even though it is implicit in contemporary psychiatric clinical practice, it is seldom stated in explicit form. What occurs in the prodromal phase of mood and anxiety disorders may affect their outcome and residual symptomatology. Certain types of co-morbidity wane with the abatement of the main disorder, whereas other types persist and may have prognostic value.

The relationship of prodromal to residual symptomatology

The assessment of subclinical symptomatology cannot be exempt from consideration of the longitudinal development of affective disorders (prodromal phase, the fully developed disorder and residual states). Detre & Jarecki (1971) provided a model for relating prodromal and residual symptomatology in psychiatric illness, defined as the rollback phenomenon: as the illness remits, it progressively recapitulates (though in reverse order) many of the stages and symptoms that were seen during the time it developed. According to the rollback model, there is also a temporal relationship between the time of development of a disorder and the duration of the phase of recovery. This has several examples in clinical medicine. For instance, *Herpes zoster* (chickenpox) has a sudden onset and quick recovery in children, whereas it

develops insidiously and tends to leave a long residual phase in adults.

Fava & Kellner (1991) suggested that prodromal symptoms may have a pathophysiological role in affective disorders and that some residual symptoms may progress to become prodromal symptoms of relapse. As a result, in unipolar major depression and bipolar disorder clinical studies concerned with prodromal symptomatology, residual states and their relationship (rollback phenomena) will be described. Each survey will be associated with pathophysiological and clinical considerations.

UNIPOLAR MAJOR DEPRESSION

Prodromes

Several studies have addressed the issue of symptom development in unipolar depression. Most of the early studies are based on clinical observations.

Hays (1964) examined prodromal symptoms in 81 patients with endogenous depression, and found that four symptoms patterns emerged: (*a*) sudden-onset depressions (associated with melancholic features and bipolar disorder); (*b*) gradual-onset depressions, where mood disorder takes months to develop and is related to common stressful life events; (*c*) neurotic-onset depressions, commonly preceded by anxiety disorders; (*d*) 'fluctuating onset' depressions, in which symptoms displayed considerable fluctuations in severity before reaching full force. Hopkinson (1965) interviewed 43 in-patients suffering from 'depressive psychosis', and found that approximately 30% showed a prodromal phase characterized by 'tension and vague feelings of anxiety' and less of the other symptoms, such as indecision and impaired concentration. Other studies dealt with the rapidity of onset of depressive symptoms. Winokur (1976) found, in a sample of 216 patients, that depression spectrum disease patients (i.e. patients who had alcoholism in first-degree relatives), were much less likely to have an acute or abrupt onset that were other depressive patients. Cadoret *et al.* (1980) found that somatic complaints and anxiety preceded the onset of depression in 117 patients in primary care. Young & Grabler (1985) reported that in 11 depressed patients a rapid onset of symptoms was associated with the endogenous subtype, the absence of past or current non-affective disorders, older age and fewer stressful life events.

Fava *et al.* (1990) investigated prodromal symptomatology occurring in the 6 months prior to the onset of depressed mood in 15 outpatients at their first episode of primary major depressive disorder. A semistructured interview based on Paykel's (1985) Clinical Interview for Depression was performed 2 to 3 months after the initial evaluations, when the patients' symptoms had improved. Family members who had observed the patient were asked to provide additional information. Each of the 15 patients reported having at least one prodromal symptom before the onset of depressed mood. Generalized anxiety was present in 13 cases and irritability in nine. Other common symptoms were: impaired work and initiative, fatigue, initial and delayed insomnia. These findings were replicated independently by Van Praag (1992) and Mahnert *et al.* (1997).

During a 6-month follow-up, after antidepressant drugs discontinuation, four of the 15 patients relapsed and required further antidepressant drug treatment (Fava *et al.* 1990). In all cases, prodromal symptoms of relapse closely resembled those of the first episode. The consistency of symptoms over time in each individual is not limited to prodromes but applies also the affective episode. Paykel *et al.* (1976) found some similarities in symptom patterns of 33 depressives between initial ratings at the height of a depressive illness and subsequent relapse several months later, after intervening recovery.

In a study associated with the NIMH Epidemiologic Catchment Area Program (Dryman & Eaton, 1991), women with sleep disturbances, diminished sexual drive, feelings of worthlessness and trouble with concentration were over five times more likely to experience an onset of major depression than those without the specified symptoms. Using the same database, Judd *et al.* (1997) found that a subsyndromal depressive syndrome (defined by two or more depressive symptoms of at least 2 weeks in duration) was frequently prodromal to episodes of major depressive disorder.

Finally, Young *et al.* (1991) studied the temporal onset of individual symptoms in winter depression and found three symptoms (fatigue, hypersomnia and increased appetite) to be

prominent in the initial phase of the episodes. They concluded that these symptoms represented the core syndrome of winter depression.

The results of these studies in unipolar depression (whether naturalistic or based on rating scales), therefore, suggest that a substantial prodromal symptomatology exists before the onset of depressed mood. Anxiety and irritability appear to dominate the clinical picture.

Residual symptoms

In 1973 Paykel & Weissman found social and interpersonal maladjustments in fully recovered depressed patients compared with controls, despite considerable improvement in social adjustment upon treatment. Submissive dependency and family attachment improved almost completely, whereas two other personal dysfunctions, interpersonal friction and inhibited communication, showed little change and greatest residual impairment (Paykel & Weissman 1973). Residual social maladjustment was subsequently reported by other investigators (Bauwens *et al.* 1991; Goering *et al.* 1992; Coryell *et al.* 1993) and was found to correlate with long-term outcome (Goering *et al.* 1992). Similarly, dysfunctional attitudes and attributions were found to persist after recovery, despite clinical and cognitive improvement (Eaves & Rush, 1984; Brown *et al.* 1990; Williams *et al.* 1990). These cognitive patterns were positively correlated with vulnerability to persistent depression or relapse (Brown *et al.* 1990; Williams *et al.* 1990; Power *et al.* 1995). These findings were consistent with the fact that vulnerable attitudes such as high neuroticism assessed when the depressed patients are symptomatic predict recovery (Scott *et al.* 1992, 1995), but when patients are asymptomatic only cognitive measures predict relapse (Williams *et al.* 1990). Social maladjustment and dysfunctional attitudes may overlap with characterological traits assessed after clinical recovery (Murray & Blackburn, 1974; Perris *et al.* 1984; Fava, M. *et al.* 1994; Peselow *et al.* 1994; Chien & Dunner, 1996; Black & Sheline, 1997; Enns & Cox, 1997; Sauer *et al.* 1997) or pre-morbid personality features (Nystrom & Lindegard, 1975; Clayton *et al.* 1994). As a result, there appears to be a residual attributional interpersonal component, which is refractory to otherwise successful treatment of depression. Such component may entail considerable predictive value.

The notion that the majority of depressed patients experience mild but chronic residual symptoms or recurrence of symptoms after complete remission, which was well delineated in the seventies (Weissman *et al.* 1976), did not receive the attention it deserved in subsequent years. Such a phenomenon was emphasized, in fact, mainly in its aetiological role with regard to dysthymia (Hirschfeld *et al.* 1986). Subsyndromal residual symptoms of major depressive disorder tended to be regarded as minor fluctuations unworthy of clinical attention. However, the presence of residual symptoms after completion of drug treatment (Mindham *et al.* 1973; Faravelli *et al.* 1986; Prien & Kupfer, 1986; Georgotas & McCue, 1989; Maj *et al.* 1992; Fava *et al.* 1994; Paykel *et al.* 1995; Judd *et al.* 1997) or cognitive behavioural therapy (Simons *et al.* 1986; Thase *et al.* 1992) in depression has been correlated with poor long-term outcome. This would parallel the fact that patients with so-called 'double depression' (major depression overlapping with dysthymia) have been shown to be less likely to make a full recovery and more likely to relapse (Keller *et al.* 1983).

Methodological problems in assessment of residual symptoms, however, emerge. There is paucity of psychometric studies addressing the phenomenology of depressed patients after benefiting from treatment. Recovered depressed patients displayed significantly more depression and anxiety than control subjects in one study (Fava *et al.* 1986), but not in another (Agosti *et al.* 1993). Differences in the sensitivity of the rating scales that were employed may account for such discrepant results. Using Paykel's (1985) Clinical Interview for Depression, only six (12·2%) of 49 patients with major depression successfully treated with antidepressant drugs and judged to be fully remitted had no residual symptoms (Fava, G. A. *et al.* 1994). The majority of residual symptoms were also present in the prodromal phase of illness. The most frequently reported symptoms involved anxiety and irritability. This was consistent with previous studies on prodromal symptoms of depression (Fava *et al.* 1990; Van Praag, 1992) and overlapped with findings concerned with interpersonal friction (Paykel & Weissman, 1973),

irritability (Nystrom & Lindegard, 1975) and anxiety (Murray & Blackburn, 1974). Using a similar methodology, Paykel *et al.* (1995), found residual symptoms to be present in 32% of 60 patients who remitted from major depression. Previous diagnosis of dysthymia did not predict residual symptoms.

In conclusion, substantial residual symptomatology appears to characterize depressed patients who successfully responded to pharmacological or psychological therapies. Anxiety, irritability and interpersonal friction appear to be common residual symptoms. Angst *et al.* (1996) observed that clinical trials overestimate the likelihood of full recovery on a single antidepressant. The usual response rates of 60 to 70% are typically reported when a reduction of 50% or more in the Hamilton Depression Rating Scale occurs. However, using a more conservative score for defining response, only 45% of approximately 900 depressed patients achieved a satisfactory response. Similarly, a major finding of the NIMH Treatment of Depression Collaborative Program was that 16 weeks of pharmacological or psychotherapeutic treatment were insufficient for most patients to achieve full recovery and lasting remission (Shea *et al.* 1992).

Cornwall & Scott (1997) recently reviewed publications relating to a precise definition of partial remission (Frank *et al.* 1991). Partial remission was found to affect at least one-third of subjects treated for depression, to increase the risk of further depressive relapse, and to affect adversely social and work performance.

Rollback phenomena

In a study by Fava, G. A. *et al.* (1994), the relationship of residual symptoms to prodromal symptomatology was specifically addressed. Almost 70% of the residual symptoms that were found to occur in 40 remitted depressed patients were present also in the prodromal phase of illness. This percentage increased to almost 90% of cases for residual generalized anxiety and irritability. The rollback phenomenon, or, at least, a strong relationship between prodromal and residual symptomatology, was thus substantiated. These results achieved independent replication (Mahnert *et al.* 1997) and are supported also by two other lines of evidence. In a prospective study (Shea *et al.* 1996), which examined the possibility that episodes of major depression result in lasting personality changes that persist beyond recovery (the scar hypothesis), there was no evidence of negative change from pre-morbid to post-morbid assessment. This would suggest continuity, whether we rate it in characterological or symptomatological terms, between the prodromal and residual phases. The second line of evidence is based on recognition of specific temporal courses of change during treatment of depression (Haskell *et al.* 1975; Katz *et al.* 1987; Casper *et al.* 1994; Nierenberg *et al.* 1995). Different types of treatment may affect the temporal course of change in depression (Watkins *et al.* 1993), and the use of pattern analysis may differentiate true drug and placebo responses early in treatment (Rotschild & Quitkin, 1992). Patients do not suddenly become well, but tend gradually to lose their depressive symptoms over the months following treatment (Keller *et al.* 1992*b*). Stassen and associates (1993) found that the time course of improvement among responders to amitriptyline, oxaprotiline and placebo was independent of the treatment modality, and thus identical in all three groups. Once triggered, the time course of recovery from illness became identical to the spontaneous remissions under placebo. Antidepressant drugs, therefore, may not change the pattern of the natural course of recovery from illness, but simply speed the recovery and change the boundary between 'responders' and 'non-responders' (Stassen *et al.* 1993).

Pathophysiological implications

An impressive body of research suggests that biological markers of depressive illness tend to subside upon clinical recovery and may accompany both prodromal and residual symptomatology. Such markers include abnormalities of the hypothalamic–pituitary–adrenal (HPA) axis (Ribeiro *et al.* 1993; Sonino & Fava, 1996), and sleep EEG patterns (Gillin *et al.* 1978; Höchli *et al.* 1986; Rieman & Berger, 1989; Buysse *et al.* 1992; Thase *et al.* 1994). In particular, abnormal dexamethasone suppression test (DST) results tend to normalize upon antidepressant treatment; failure to do so is often associated with a poor prognosis, indicating that fully recovery from depression should include normalization of the HPA axis (Fava & Sonino, 1986). As a result, persistent non-suppression, despite antidepressant treatment,

or reversion to abnormal DST results, may be prodromal signs of relapse in unipolar depression. Similarly, EEG sleep abnormalities have been associated with high relapse rates (Giles *et al*. 1987; Reynolds *et al*. 1989; Kupfer *et al*. 1990). Furthermore, a number of sleep abnormalities, including reduced REM latency, decreased slow wave and reduction in sleep-related growth hormone secretion, have been found to persist for several months after clinical remission (Hauri *et al*. 1974; Rush *et al*. 1986; Jarrett *et al*. 1990; Kupfer *et al*. 1990). However, there has been insufficient emphasis on the relationship of biological markers such as sleep EEG and DST findings and the residual symptomatology of unipolar depression (Rieman & Berger, 1989; Rotschild *et al*. 1993). For instance, a high incidence of resistance to dexamethasone suppression was documented among recovered patients with a high number of depressive episodes (Gurguis *et al*. 1990). Since a temporal lag exists between biological abnormalities and clinical symptomatology in depression (Ribeiro *et al*. 1993). persistence of markers may simply indicate incomplete remission, and thus vulnerability to relapse. The lack of any abnormal sleep EEG findings in a group of remitted patients free of residual symptoms and psychoactive medication for a long period of time (Rieman & Berger, 1989), would be in line with this hypothesis.

Therapeutic implications

There has been increasing awareness of the bleak long-term outcome of depression with regard to relapse and recurrence (Ormel *et al*. 1993; Piccinelli & Wilkinson, 1994; Surtees & Barkley, 1994; Labbate & Doyle, 1997). Ramana *et al*. (1995) reported on the course of depression with respect to remission and relapse in a 2-year prospective follow-up. Remission was rapid with 70% of subjects remitting within 6 months and only 6% failing to do so by 15 months. However, 40% relapsed over the subsequent months, with all relapses occurring during the first 10 months. This unfavourable outcome seems to parallel the presence of substantial residual symptomatology in patients judged to be remitted and no longer in need of active treatment. Indeed, residual symptoms, as well as persistence of altered biological markers such as the dexamethasone suppression test, are probably the most consistent predictors of relapse. In a large cohort study, asymptomatic recoverers relapsed in 157 weeks, compared with residual recoverers who relapsed in about 28 weeks (Judd *et al*. 1997). Furthermore, residual symptomatology meeting the criteria for subsyndromal depressive symptoms was associated with a significantly increased prevalence of past histories of major depressive episodes and an elevated lifetime prevalence of suicide attempts (Judd *et al*. 1997). Since prodromal symptoms of relapse appear to mirror those of the initial episode (Fava *et al*. 1990), an early recognition of prodromal symptoms could be valuable. Kupfer *et al*. (1989) outlined the clinical advantages of early treatment intervention in recurrent depression. Early treatment might shorten the episode, prevent suffering, and perhaps require lower dosages than the treatment of the advanced stage of the disorder.

However, the challenge in the treatment of depression today appears to be the prevention of relapse more than the attainment of recovery. And the question arises as to whether reduction or disappearance of residual symptomatology may entail a more favourable long-term outcome of depression. A preliminary answer to this question was provided by a controlled therapeutic trial (Fava, G. A. *et al*. 1994, 1996). Forty patients with major depressive disorder who had been successfully treated with antidepressant were randomly assigned to either cognitive behavioural treatment or clinical management of residual symptoms. In both groups, antidepressant drugs were tapered and discontinued. The group that received cognitive behavioural treatment had a significantly lower level of residual symptoms after drug discontinuation compared with the clinical management group. Cognitive behavioural treatment also resulted in a lower rate of relapse, with the achievement of statistical significance at a 4 year follow-up (Fava *et al*. 1996).

Attention has been called to the arbitrary nature of the distinction between treatment response associated with residual symptomatology and refractory depression (Fava, 1996). Refractory depression is a clinical problem that may occur in as many as 30% of depressive episodes, but only recently has attracted adequate attention (Fava, M. & Davidson, 1996; Ananth, 1998). An open trial of 19 patients who

failed to respond to at least two trials of antidepressant drugs of adequate dosages and duration and were offered cognitive behavioural treatment (Fava *et al.* 1997) replicated the findings obtained with treatment of residual symptoms. Most of the 12 patients who responded had no or few residual symptoms upon recovery and only one relapsed at a 2-year follow-up.

There is increasing awareness of the fact that current forms of treatment seem to be insufficient for many patients, both in adult (Shea *et al.* 1992) and adolescent (Bartlett *et al.* 1991) depression, to achieve full recovery and lasting remission. Neglect of subclinical symptomatology in formulating a treatment plan may affect the inadequate or simply partial treatment which patients may receive, even in specialized settings.

BIPOLAR DISORDER

Prodromes

Kraepelin (1921) described the prodromal phase of acute mania as follows: 'The beginning of the illness is always very sudden; at most headaches, weariness, lack of pleasure in work or a great busyness, irritability, sleeplessness, precede by some days or weeks the outbreak of the more violent manifestations…'. Indeed a rapid build-up of mania (typically in 1–7 days) was subsequently confirmed by studies of NIMH inpatients (Bunney *et al.* 1972; Carlson & Goodwin, 1973; Post *et al.* 1981). Winokur (1976) studied the onset of bipolar episodes, defined as the period of time that transpires between the development of symptoms and the point at which the patient enters a study at the time of hospital or clinic admission. He observed a significantly more rapid onset of mania than bipolar or unipolar depression. Other investigations suggested a more rapid onset of bipolar depression compared to unipolar episodes (Hays, 1964; Young & Grabler, 1985).

Molnar *et al.* (1988) investigated duration and symptoms of bipolar prodromes in 20 outpatients receiving lithium prophylaxis, who were clinically stable, by means of a semi-structured interview, whose reliability was cross-checked. The duration and symptoms of manic and depressive prodromes showed substantial variation among patients. Unlike previous studies, manic prodromes were significantly longer than the depressive prodromes. The most frequently reported depressive symptoms were depressed mood, loss of energy and difficulty in concentrating. As for manic episodes, it was striking that all patients reported increased activity as a prodromal symptom. Elevated mood and decreased need for sleep were also common. Within each patient, there was a striking consistency in prodromal symptoms preceding each episode; that is, affective episodes in individual patients tended to begin according to consistent sequences.

Subsequent, independent investigations confirmed that there are consistent sequences of symptoms preceding manic or depressive relapses in bipolar patients (Altman *et al.* 1992), that the duration of manic prodromes was longer than that of depressive prodromes (Smith & Tarrier, 1992), the presence of an interval between first symptoms and peak severity (Francis & Gasparo, 1994) and that the majority of patients could identify prodromal symptoms as confirmed by relatives (Sclare & Creed, 1990; Keitner *et al.* 1996). Furthermore, atypical depression was found to be a precursor of bipolar disorder (Ebert & Barocka, 1991).

Residual symptoms

Several studies (Donnelly *et al.* 1976; MacVane *et al.* 1978; Kerry & Orne, 1979; Lumry *et al.* 1982; Bouman *et al.* 1992), failed to detect significant differences between remitted bipolar patients on lithium prophylaxis and normal control subjects. The lack of differences between patients and controls may be due to the use of inadequately sensitive rating scales and to methodological flaws (Fava, 1992*a*). Other studies on remitted patients with bipolar disorder receiving prophylactic lithium showed in fact that they experience significantly more psychological distress and less well-being than control subjects (Fava *et al.* 1984, 1987). Psychological distress also included hostility and irritable mood, confirming Mayer-Gross' original observations (1937). In another study (Cooke *et al.* 1996), scores concerned with well-being and functioning of 68 euthymic outpatients were often in the range of patients with chronic medical illness and major depression. Also, Keitner *et al.* (1996) found residual mania in about 70% of their cases and residual

depression in about 60%. These figures represent high rates of clinical symptomatology, even though patients appeared to have recovered. Finally, considerable subclinical fluctuations emerged with longitudinal design (Goodnick *et al*. 1987; Molnar *et al*. 1987; Dion *et al*. 1988). These findings are consistent with the socio-economic (Dion *et al*. 1988), psychosocial (Coryell *et al*. 1993) and clinical (Maj *et al*. 1989; Tohen *et al*. 1990; Solomon *et al*. 1995; Strober *et al*. 1995; Coryell *et al*. 1997) deterioration of patients on lithium prophylaxis during the course of illness. Residual symptoms after remission appeared to be correlated with social maladjustment (Bauwens *et al*. 1991). It is difficult, however, to establish wether characterological traits affect social adjustment and functional recovery or both personality and social dimensions reflect subclinical bipolar symptomatology that is not included in other symptom measures. However, the presence of personality disturbances on remission (Strakowski *et al*. 1993; Osher *et al*. 1996; Solomon *et al*. 1996) and of subsyndromal fluctuations (Keller *et al*. 1992*a*) were found to increase risk of relapse in bipolar disorders. Patients with bipolar disorder who were given lithium carbonate to achieve low-range levels (0·4 to 0·6 mmol/l) had 2·6 times the risk of relapse as those given lithium for standard-range levels (0·8 to 1·0 mmol/l) and nearly twice the risk of developing subsyndromal symptoms (Keller *et al*. 1992*a*).

Rollback phenomena

A substantial overlap between prodromal and residual symptoms in bipolar disorder was reported by Keitner *et al*. (1996). Prodromal symptoms, however, outnumbered residual symptoms as reported by both patients and family members. Cognitive symptoms were consistently the most common type of symptoms reported, except in the instance of prodromal mania.

The conceptual model that emerges from studies on subclinical symptomatology of bipolar disorder suggests that most patients are symptomatic most of the time. Episodes are only the most pronounced peaks of such symptomatology, that is substantially reduced, even though not eliminated, by mood stabilizing drugs. Their progressive loss of efficacy – as well as the deteriorating outcome of illness – may be explained on the cumulative effects of subclinical symptoms. It should be noted, however, that these studies were performed in specialized settings, where a higher degree of severity may be expected. Results may be different in general practice.

Pathophysiological mechanisms

Post's conceptual model of kindling has achieved a prominent role in the neurobiology of bipolar disorder (Post, 1992). The kindling and sensitization models are based on the occurrence of syndromic affective episodes, which propel the illness toward autonomy. Yet, subclinical fluctuations of mood in bipolar disorder may play a considerable role in affecting the balance between pathological and compensatory mechanisms, as suggested by the strong relationship between subsyndromal fluctuations and likelihood of relapse (Keller *et al*. 1992*a*). The pathophysiological mechanisms discussed for unipolar depression may apply also to bipolar patients. Carroll (1994) provides a helpful conceptualization of the brain mechanisms whereby mood shifts may occur. Court's continuum theory (1968), in which depression constitutes the first level of breakdown and mania a more severe condition, is also helpful in this context. Not only the intensity of the affective episode, but also its duration (even in subclinical and mild forms) may be important in increasing vulnerability to bipolar disturbances. Progressive loss of non-symptomatic inter-episode functioning, whether due to pharmacological disruption of receptor balances (antidepressant induced cycle acceleration) or psychosocial stress, may prevent adequate compensatory mechanisms for patients with bipolar disorder.

Treatment implications

Bipolar disorder appears to be characterized by 'a malignant course in which frequent recurrences are accompanied by significant symptoms between episodes' (Solomon *et al*. 1995). Because of the high proportion of patients who fail to respond to lithium only, supplementary medications may be required. Since the appearance of prodromal symptoms may precede the full syndrome by weeks or months, if patients and their family members are educated to recognize the patient's characteristic prodromal

symptoms, recurrences of affective disorder could be treated earlier and perhaps more effectively (Molnar *et al.* 1988). In a first episode, it seems unlikely that either the patient or the relative could recognize the prodromal phase unless it was strikingly different from the patient's usual mood and appeared to be ominous. However, this becomes feasible in subsequent episodes, particularly since prodromal symptoms tend to be consistent within the same individual, Jacobson (1965) described a programme for the early detection and control of hypomanic episodes, based on appraisal of individual prodromal symptoms and intermittent use of lithium. Case reports of intermittent clinician administered (Molnar & Fava, 1989) or self-administered use of lithium (Terao, 1993) have also been described.

Whether additional pharmacological strategies supplementing the traditional pharmacotherapy may be of value in reducing residual symptomatology in bipolar disorder is an issue worthy of investigation. There is paucity of studies on the psychotherapeutic approach to bipolar illness (Colom *et al.* 1998). It would be of interest to verify whether cognitive behavioural treatment may decrease residual symptomatology and occurrence of relapse in bipolar disorder, as was found in unipolar depression. The development of a specific psychotherapeutic strategy is an important step in this direction (Ramirez & Rush, 1996). Segal *et al.* (1996) offered an interesting cognitive science perspective on kindling and episode sensitization in recurrent affective disorder. Vulnerability to depressive relapse would be determined by an increased risk of particular negative patterns of information processing being activated in depressed states. Such processes may have biological correlates, e.g. hormonal (Fava *et al.* 1985; Vieta *et al.* 1997). The prediction of depressive relapse in a remitted bipolar patient by CRF challenge test (Vieta *et al.* 1997) parallels that achieved by psychometric methods (Strakowski *et al.* 1993).

CONCLUSIONS

Appraisal of the literature on subclinical symptoms of mood disorders challenges the view that only syndromes requiring specific intensity thresholds are worthy of clinical attention. Its main implications may be summarized as follows.

1 A prodromal phase can be described in most instances of mood disorders. This calls for a reassessment of basic pathophysiological models of pathogenesis of unipolar depression and bipolar disorder. Such models, in fact, neglect intermediate phenomenological steps in the balance between health and disease. The pathophysiological model that is entailed by the existence of a prodromal phase is in line with the concept of allostatic load, defined as the cost of chronic exposure to fluctuating or heightened neural activation (McEwen & Stellar, 1993).

2 Standard treatment of mood disorders, even in specialized settings, seems to leave a large amount of residual symptomatology, which appears to be one of the strongest predictors of unfavourable outcome in unipolar depression. The literature on residual symptomatology calls for a reassessment of the concept of recovery and provides a welcome antidote against excessive optimism as to the effectiveness of psychiatric interventions, particularly in current times of pharmacological oversimplification (Fava, 1995).

3 There appears to be a relationship between residual and prodromal symptomatology (the rollback phenomenon). Certain prodromal symptoms may be overshadowed by the acute manifestation of the disorder, but persist as residual symptoms and progress to become prodromes of relapse. Prodromal symptoms of relapse, both in unipolar depression and bipolar disorder, tend to mirror, in fact, those of the initial episode.

4 At times, residual symptoms may be subsumed under new, independent rubrics. Manu *et al.* (1996), for instance, found that chronic fatigue syndrome is often part of residual depression in partial remission. In the same vein, dysthymia appears to be more closely related to major depression (Paykel, 1994) than has sometimes been argued.

5 In view of very high rates of relapse and recurrence, long-term continuation and maintenance therapies for depression have become increasingly important (Fava M. & Kaji, 1994). Combining different treatment modalities (e.g. pharmacological and psychotherapeutic) has been advocated, yet with modest results (Wexler & Nelson, 1993). The literature on subclinical

symptoms highlights the importance of administration of treatment in sequential order. Some preliminary evidence would suggest that specific treatment of residual symptoms in depression may improve long-term outcome, by acting on those residual symptoms that progress to become prodromal symptoms of relapse (Fava *et al*. 1996). It is also conceivable that psychotherapeutic strategies may decrease subclinical symptomatology in patients with bipolar disorder who are receiving lithium treatment, and, by doing this, may improve long-term outcome.

6 A largely untested assumption in unipolar depression is that therapeutic strategies (particularly pharmacological) that are effective in the short-term are the most suitable for post-acute and residual phases or maintenance. The literature on subclinical symptomatology calls for specific, stage orientated therapeutic approaches (Fava, 1997).

7 Even though there may be overlap between subclinical symptoms and personality traits, a distinction is feasible on the basis of the quality and characteristics of symptoms. Unlike characterologic traits, subclinical symptoms pertain to the list of disturbances that are present and characterize the acute manifestation of a disorder, have a specified onset, and are amenable to treatment. The study of prodromal and residual symptoms of mood disorders thus entails considerable clinical implications for everyday practice, whereas the personality and temperament constructs have failed to yield such information, despite extensive explorations.

8 Ryff & Singer (1996) remark that, historically, mental health research is dramatically weighted on the side of psychological dysfunction and that health is equated with the absence of illness rather than the presence of wellness. They suggest that the absence of well-being creates conditions of vulnerability to possible future adversities and that the route to recovery lies not exclusively in alleviating the negative, but in engendering the positive. Little is known on the relationship between subclinical symptoms and well-being in the residual phase of affective disorders. In a preliminary investigation (Fava *et al*. 1998), a well-being enhancing psychotherapeutic strategy (well-being therapy) was found to be associated with a significant reduction in residual symptoms in patients with affective disorders. The balance between positive and negative affects and its biological counterparts may thus carry a considerable weight on the complex regulation underlying long-term outcome of affective disorders.

Despite the relative neglect of research on subclinical symptoms of mood disorders, the reports summarized in this article, therefore, address important clinical issues that deserve further study and may be of immediate practical value. They provide challenging insights in the pathogenesis and course of mood disorders, which may result in therapeutic efforts of more enduring quality than current strategies.

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